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On 8 June 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Sette *et al.*

Application No.: 09/017,743

Filed: February 3, 1998

For: HLA BINDING PEPTIDES AND THEIR USES

Examiner: M. DiBrino

Art Unit: 1644

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Communication mailed May 8, 2000, Applicants submit the following Group election and election of species as detailed below with traverse.

Election of Invention

The Requirement for an Election of a Group is traversed. Restriction of an application is discretionary, as a restriction requirement is made only to avoid placing an undue examination burden on the Examiner and the PTO.

The two Groups set forth by the Examiner are:

Group I, claims 8-10, 17-27, 28-30, 36-46, and 66-70, drawn to an isolated nucleic acid encoding a peptide and a pharmaceutical composition classified in class 536, subclass 23.5

Group II, claims 11-16, 31-35, and 47-65, drawn to an isolated nucleic acid encoding a peptide polymer, classified in class 536, subclasses 23.1 and 23.72.

Applicants submit that the restriction requirement is improper because the Group II claims only vary the breadth or the scope of the invention defined in Group I claims and further, that searching all of the claims together does not present an undue burden on the Examiner.

A. The Group election requirement is improper.

The MPEP at § 806.03 states:

> Where the claims of an application define the same essential characteristics of a *single* disclosed embodiment of an invention, restriction therebetween should never be required. This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition.

The Group election requirement is improper because the claims categorized in Group II merely vary in breadth or scope of definition of the invention as claimed in Group I claims. For example, Group II claims 11-16 depend from Group I claim 8. The open-ended "comprising" term set out in claim 8 clearly encompasses addition of other elements to the claims. Claims 11-16 vary the breadth of the embodiment set out in claim 8 by further defining the "other elements". Similarly, Group II claims 31-35 depend from Group I claim 28 and further define the embodiment set out in claim 28. Thus, claims 11-16 and 31-35 *modify* the breadth of the independent claims 8 and 28, but define the same essential characteristics, a nucleic acid encoding a supermotif-bearing "starting" peptide as claimed in claims 8 and 28. The Examiner's assignment of these claims into separate Groups is therefore improper.

Claim 47 is also essentially drawn to a nucleic acid encoding a starting peptide as set out in claim 8, but a starting peptide that is further defined by additional claim elements, such as those recited in claims 11 and 12. Thus, claim 47 (and its dependent claims 48-65) is a different definition of the same invention that varies in breadth or scope of definition. Accordingly, all of the claims should be examined together.

B. No undue burden is required to examine all of the claims together.

No undue burden is imposed by examination of all of the claims together. The subject matter of the Group II claims is encompassed by a proper search that is appropriate to the scope encompassed by the comprising language of the Group I claims, particularly independent claims 8 and 28. For example, an effective search for prior art of potential relevance to claims 8 and 28 must accommodate the comprising language and therefore will include additional elements, *e.g.*, those recited in claims 11-16 and 31-35. Moreover, claim 47 encompasses the subject matter set out in claim 8 and further incorporates limitations such as those of claims 11-12, into the independent claim. Thus, a proper search of the Group I claims will include the subject matter set out in all of the claims. Accordingly, examination of all of the claims of Groups I and II together does not place an undue burden on the Examiner.

Furthermore, although the Examiner has assigned Groups I and II to the same Class, but different subclasses, the designation of the different subclasses appears to be completely arbitrary. Applicants respectfully suggest that, based on the definitions of the subclasses, all of the claims are properly assigned to the same subclass. Subclass 23.5 includes sequences that encode an animal polypeptide and further refers to subclass 23.1, DNA or RNA fragments or modified form thereof. Subclass 23.72 includes viral proteins and further refers to subclass 23.7, which includes compounds that are DNA fragments which encode specific viral proteins.

Each of the Groups includes claims that recite an isolated nucleic acid molecule comprising an immunogenic peptide, *i.e.*, a starting peptide. The only distinction between Group I and Group II claims is that the Group II claims recite nucleic acids that comprise limitations in addition to the starting peptide, which limitations are included in the open-ended comprising term of the Group I claims. Thus, all of the claims include sequences that encode animal polypeptides and all of the claims are drawn to DNA or RNA fragments. Accordingly, all of the claims are properly assigned to the same subclass.

C. Formal election

In view of the foregoing remarks, Applicants respectfully request withdrawal of the restriction requirement. As a formal matter, but with traverse, Applicants elect Group I, claims 8-10, 17-27, 28-30, 36-46, and 66-70.

Species Election

Overview

The pending claims are directed to methods of making immunogenic peptides. The Examiner has required election of a single species through multiple layers of specified characteristics. The myriad elections are traversed.

In order to facilitate an evaluation of the requirements set forth in Paper 16, a representative generic claim, for example claim 8, is presented below:

> 8. An isolated nucleic acid molecule comprising:
>
> a non-naturally occurring nucleic acid encoding an immunogenic peptide, said immunogenic peptide comprising an epitope consisting of about 8-11 residues which comprises a structural supermotif associated with peptide binding to multiple HLA molecules, said structural supermotif comprising a first amino acid anchor residue at a position two from the epitope's amino-terminal amino acid residue, said first anchor residue consisting of P, and a second amino acid anchor residue selected from the group consisting of V, I, L, F, M, W, Y, and A as the epitope's carboxyl-terminal amino acid residue;
>
> wherein the immunogenic peptide induces a cytotoxic T cell response when in complex with an HLA molecule and is contacted with an HLA-restricted cytotoxic T cell.

As discussed in more detail below, Applicants submit that the multi-layered species election set forth in Paper 16 disregards key aspects of the invention and does not provide for examination of the invention as disclosed and claimed by the Applicants. Although some type of species election may be reasonable under the circumstances, the election requirements of Paper 16 are not. A reasonable species election should be based on the invention as disclosed and as claimed by the Applicants in the generic claims. Accordingly, any species election should focus on the elements provided in those claims,

which relate to an HLA class I supermotif pattern of amino acid residues that is associated with binding multiple specified HLA molecules. Any appropriate species are delineated by one or more patterns defined by the claimed supermotif. Accordingly, Applicants propose that an appropriate species election should be directed to species encompassed by a defined amino acid of P at a position two of an epitope together with the collective examination of the amino acid residues that have been defined for the supermotif at the C-terminus of an epitope. Moreover, the proposed election does not present an undue burden for the Examiner.

The species election requirement as set forth is also extremely confusing. It does not apprise the Applicants how examination of the claims will proceed once an initial species is selected and is determined to be free of the prior art, nor does it enlighten the Applicants as to the strategies that might be employed to make elections. The Applicants thus have no assurance that the invention as they have disclosed and claimed it will be examined.

Discussion

The election of species detailed in Paper 16 requires the Applicants to elect a representative from the extensive list of the following criteria:

a.) a nucleic acid encoding a specific species of peptide and motif disclosed in the specification ; and

b.) a peptide of 8, 9, 10, or 11 amino acid residues in length; and

c.) a cancer-associated antigen or a pathogen-derived peptide; and

d.) if a cancer-associated antigen is selected, one patentably distinct species of antigen, *e.g.*, MAGE2, p53, HER2/neu, CEA or prostate; or if a pathogen-derived peptide is selected, one patentably distinct species of antigen, *e.g.*, HBV, HCV, HIV, or malaria; and

e.) a specific HLA molecule, i.e., a specific HLA molecule recited in claim 17, 36, or 55; and

f.) a peptide having an IC_{50} of less than about 500 nM or of less than about 50 nM for an HLA molecule; and

g.) If Group II is elected, a single disclosed species of "additional peptide" wherein the additional peptide is a T helper epitope or a CTL epitope.

Applicants respectfully submit that the incredibly detailed dissection of the claimed subject matter is not justified. The species election requires that Applicants make choices that are directed to mere characteristics of embodiments and detract from the actual invention, *i.e.*, a nucleic acid encoding an immunogenic peptide comprising an epitope defined by a supermotif associated with binding to multiple HLA molecules, intended by Applicants to be the focus of their application as properly claimed by the Applicants in their independent claims. A less onerous species election could have been required, and no unduly extensive and burdensome search would be necessary (MPEP § 808.01(a)). Accordingly, as will be explained, the claims should be examined as a whole or in a far less dissected manner.

A. The multi-layered election of species is confusing.

Applicants find the species election extremely confusing. Moreover, Applicants have not been able to ascertain how the Examiner will proceed with the examination of the application upon a determination that an initially elected "species" that conforms to all of the election requirements is free of the prior art. Will the determination of the next species to be examined be made based on the sequence of the peptide, the length of the peptide, the antigen from which the peptide is derived, the HLA molecule(s) to which the peptide binds? This presents a major concern to the Applicants because they are not able to ascertain basic parameters of the examination and thus determine a suitable prosecution strategy. Furthermore, each time a new species is selected, various aspects of the invention are omitted at what seems to be an arbitrary choice of the Examiner (discussed in Section B., below). Under the traversed requirement of Paper 16, the ultimate nature of the invention thus appears to be defined not by the Applicants, but by the Examiner. Hence, it is evident that implementation of the species election requirements imposed by the Examiner would cause the loss of Applicants' right to pursue their invention as claimed and, thus, should be withdrawn.

B. Examination of a single species with multiple levels of characteristics conforming to the election requirements disregards important aspects of the invention as claimed.

It is improper for the Office to refuse to examine that which applicants regard as their invention (MPEP § 803.02, relating to Markush claims). Though the subject restriction

requirement is for a species election which does not *per se* preclude examination of the scope of the generic claims in this application, the multi-layered species election could have undue and harsh consequences. The dissection of the claims in the manner of the Office Action could potentially prolong prosecution by directing focus to less critical characteristics that may not even be significant elements of the actual invention. For example, where a nucleic acid encoding a single peptide is examined, the "supermotif" aspect of the invention is not being examined. The supermotif is a key aspect of Applicants' invention as reflected by the generic independent claims. "[T]he scope of subject matter of an invention is governed not by the examiner's conception of the invention, but by that which the applicant regards as his invention" *In re Wolfrum* 179 USPQ 620 (C.C.P.A. 1973) (addressing a 35 U.S.C. § 112 rejection).

Thus, Applicants maintain that requiring election among numerous characteristics set forth in Paper 16 ignores critical aspects of the invention as disclosed and claimed in the generic claims, such as claim 8 provided above. The generic claims relate to nucleic acids encoding immunogenic peptides that are conceptually bound together by a commonality of function, operation and effect. The claimed methods are directed to nucleic acids encoding an immunogenic peptide comprising an epitope *having a specified supermotif or residue pattern associated with binding to multiple HLA molecules, wherein the peptide is immunogenic and induces a cytotoxic T cell response in the context of the multiple HLA molecules to which the peptide binds.* Thus, Applicants' invention is truly generic in that it covers supermotif patterns present in any peptide sequence that can be bound by multiple HLA molecules and thereafter induce CTL responses, and is appropriately examined on a generic level. The claimed invention is not simply a list of nucleic acids encoding peptides of unrelated sequences and is not in any way constrained by parameters such as antigenic source or length of an HLA Class I epitope (as discussed in detail at a recent Examiner interview with Examiners Schwartz, Chan, Schwadron and former Examiner Cunningham). Consequently, the dissection of the invention by the multi-layered election requirement loses sight of the actual invention and is tantamount to a recharacterization of the invention.

Applicants also respectfully point out that the examination of claims in the pending application based on the species election set forth in Paper 16 can yield results that are

incongruous with the policy set forth in the MPEP at § 803.04. The species election requirement could result in the examination of a fewer number of actually related sequences than if the claims were such that they fell within the policies of MPEP § 803.04 and were sequences that were completely unrelated.

The generic claims in this case focus on amino acid supermotif patterns present in immunogenic peptide epitopes. Accordingly, Applicants propose that it would be appropriate to make a species election requirement based on the elements provided in the generic claim, namely of species defined by one or more supermotif patterns, in accordance with MPEP § 803.02. A species election consonant with MPEP policies would involve election of individual species as follows: a species encompassed by the specific amino acid P at residue two of an epitope together with the amino acid residues that have been defined for the supermotif at a C-terminus of an epitope (V, I, L, F, M, W, Y, or A, at one of positions 8, 9, 10, or 11). Examination of the supermotif in this manner provides for not more than 32 species. Thus, this proposed species election requirement is properly directed to the motif aspect of the invention set forth by the generic claims and focuses on the invention as a whole.

C. No undue examination burden is imposed by examining all C-terminal positions together.

Furthermore, for a given supermotif, no undue examination burden is imposed by examining P at position two and V, I, L, F, M, W, Y, or A residue at each of positions 8, 9, 10, and 11, *i.e.*, the C- terminus of HLA class I epitopes. Computer searching techniques readily permit the searching of amino acid sequences with designated amino acids at positions of choice. Such a search is not unduly extensive, but is thorough and properly includes the relevant supermotif species of a P residue at a position two and any of V, I, L, F, M, W, Y, or A at the C terminal position of an epitope. The species defined in this manner number no more than 8. Moreover, for teachings related to peptides that bind to HLA class I molecules, it is prudent to consider C-terminal positions of epitopes which are 8, 9, 10, or 11 residues long, to get a truly comprehensive view of this art. Logic dictates that a typical computer search of the claimed supermotif would necessarily reveal any art related to methods of making immunogenic peptides of different lengths. The search would also reveal that HLA class I supermotif technology is not tied to any particular antigen, whether a cancer-associated antigen

or a pathogenic agent and furthermore, certainly would not be restricted by the other multitudinous characteristics set forth in Paper 24.

The species election detailed in the Paper 16 results in a division of Applicants' actual invention into an artificially voluminous and unreasonable number of "species" or more accurately, characteristics. An election requirement that defines a species as a nucleic acid encoding an immune peptide comprising an epitope characterized by a supermotif pattern associated with binding to multiple HLA molecules constitutes a "reasonable number" of species for examination, and thereby balances the rights of the inventor and the administrative concerns of the Patent Office. An appropriate number of species, as discussed above, is: (i) 32, *i.e.*, P at position two of an epitope in combination with each residue (V, I, L, F, M, W, Y, or A) at a C-terminal position of an epitope of 8, 9, 10, or 11 in length; or (ii) more appropriately 8, *i.e.*, P at position two and each residue defined for the C-terminal position of an epitope.

D. Election

In view of the foregoing remarks, Applicants respectfully request withdrawal of the species restriction requirements. As a formal matter, Applicants elect, with traverse, the following species with the understanding that upon the determination that the elected species is free of the prior art, additional species will be examined in accordance with MPEP § 803.02, which states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." and that "The prior art search will be extended to the extent necessary to determine the patentability of the Markush-type claim."

Accordingly, as a formal matter, Applicants elect:

a nucleic acid encoding the peptide FPIPSSWAF and the motif P at position 2 and F at the carboxy terminal position; and a nucleic acid encoding a peptide of 9 residues in length; and a nucleic acid encoding a peptide derived from a pathogenic agent and an antigen of interest that is an HBV antigen, and a specific HLA molecule recited in claims 17, 36, or 55 that is HLA-B*0701, and a nucleic acid encoding a peptide having an IC_{50} of less than 500 nM for an HLA molecule; and, if the Group election requirement is withdrawn and the species

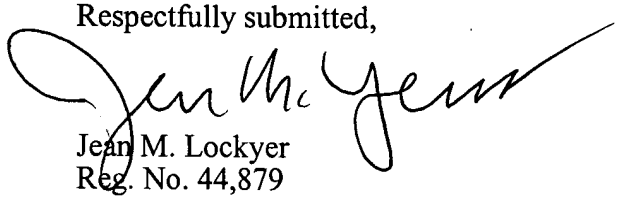
restriction of section 10 of Paper 16 applied to all of the claims, a nucleic acid comprising an additional peptide that is a CTL epitope.

All of the species elections are made with traverse for the reasons set forth herein. The pending Group I claims that read on the elected species are claims 10, 17, 20-27, 30, 36, 39-46, 67-70, and independent claims 8, 28, and 66. If the Group election requirement is withdrawn by the Examiner and the species restriction applied to all of the claims, including the restriction of section 10 of Paper 16, the claims that read on the elected species are: claims 10, 12, 14, 15, 16, 17, 20-27, 30, 32, 34-36, 39-46, 49, 52-55, 58-65, 67-70 and independent claims 8, 28, 47, and 66.

CONCLUSION

If the Examiner has any questions regarding this communication, or if the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200 or the in-house Attorney for Applicants Timothy J. Lithgow at 858-860-2514.

Respectfully submitted,



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